REMARKS

Claims 21-38 are currently pending and stand rejected. Claim 21 has been amended to expressly recite that step (b) occurs following step (a). As explained below, this requirement was implicitly present in the previously pending claims and therefore raises no new issue, adds no new matter, and does not require any additional searching on the part of the Examiner. Furthermore, Applicants note that the amendments place the application in better form for appeal by simplifying the issues for appeal. As such, the amendment's entry after a final rejection is appropriate and Applicants respectfully request the same. Support for the amendment can be found throughout the claims and specification, for example, in original Claim 10, the abstract, and paragraphs 0011, and 0079-0081.

The sole issue in the Final Office Action is whether the pending claims are obvious over the Examiner's proposed combination of Zanzucchi et al. (U.S. Pat. No. 5,593,838) in view of Okano et al. (5,607,646) and Brenner (U.S. Pat. No. 5,962,228).

The Examiner has asserted that Zanzucchi discloses a method of isolating polynucleotides from a mixture via a serial array of wells where the wells include beads that can have DNA material bound to their surface and the wells can be heated and cooled. The Examiner has asserted that Okano teaches the use of heating and electric fields for elution of specific polynucleotides and that Brenner teaches an array formed of microparticles having tag components. The Examiner has asserted that "it would have been obvious...to have combined the microparticles of Brenner in the individual cells of the array of Okano with the series of wells/array of Zanzucchi et al., whereby the device would be used in a polynucleotide assay whereby specific binding reactions can take place at selected supports and eluted from same, and that the mixture would flow in a serial fashion through each of the solid supports." (Final Office Action, page 6). Applicants respectfully traverse.

Present Claim 21 recites the following:

> 21. A method for isolating one or more different-sequence polynucleotides from a mixture, the method comprising:
>
> (a) flowing the mixture through a flow path containing a plurality of solid supports which are located in series in the flow path, such that the mixture flows serially through each of the plurality of solid supports, each support having bound thereto a sequence-specific capture agent complementary to a different-sequence polynucleotide, under conditions effective to specifically bind different-

sequence polynucleotides to corresponding sequence-specific capture agents on one or more of the supports,

(b) after step (a), releasing bound polynucleotides from a selected support by altering a physical property of that support while leaving unaltered the same physical property of at least one other of the supports, wherein the physical property is temperature, and wherein said releasing is accomplished by heating a first solid support; and

(c) eluting the released polynucleotides through the flow path such that the eluted polynucleotides can be isolated in separated form. (emphasis added)

As the Examiner is aware, several criteria must be met in order to establish a *prima facie* case of obviousness. First, the prior art references must teach all the claim limitations. Second, the Examiner must demonstrate that one of skill in the art would have reasonably expected the proposed combination to work. (M.P.E.P. §2143). Finally, there must be a reason to combine the various elements. (*KSR Intl. v. Teleflex Inc.* (U.S. Supreme Court, April 2007)). Furthermore, in the Court's recent decision in *KSR*, the Court reaffirmed the importance of the Graham factors in determining obviousness, which includes four factual inquires that must be performed. One must (A) determine the scope and content of the prior art, (B) ascertain the differences between the prior art and the claims in issue, (C) resolve the level of ordinary skill in the pertinent art, and (D) evaluate evidence of secondary considerations. (*Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)).

As explained below, the cited art does not teach all of the elements in the claims and lacks sufficient scope and content to make the claimed combination obvious. Additionally, the various differences between the cited art and the claimed invention are significant and meaningful. In fact, some of the cited art actually teaches away from the Examiner's proposed modifications or combinations of the elements, further emphasizing the differences and demonstrating strong evidence of nonobviousness as a secondary consideration. Finally, the Examiner's proposed reasons to combine the various references are faulty and even improper in various respects. As such, Applicants submit that the claimed invention is nonobvious. Each of these issues is addressed in more detail below. Following this analysis, Applicants have also summarized the clear legal errors and factual mistakes made by the Examiner in the most recent Final Office Action and have included a section of clarifying remarks in regard to the previous response.

A. The Cited References do Not Teach all of the Recited Elements

The References do not teach the recited steps of step a) and then step b) in Claim 21

The Examiner has asserted that Zanzucchi discloses using an array of wells in serial fluid connection. However, the presently claimed method recites more than simply flowing a mixture through a series of wells where binding, release, and elution can occur randomly during the process. Claim 21 recites a method of flowing the mixture through each of the plurality of solid supports before one releases bound polynucleotides from the selected supports. Applicants note that this was previously recited in Claim 21 which required that step b) occur "after said specific binding" which occurs at the end of step a), which occurs following flowing the mixture "serially through each of the plurality of solid supports...." In order to explicitly recite this feature, Applicants have amended step (b) to explicitly note that step (b) occurs "after step (a)".

In contrast, Zanzucchi (and presumably the Examiner's proposed combination as the Examiner did not address this issue in the Final Office Action) teaches that the flow of the mixture through each of the wells (which would each contain a solid support in the Examiner's proposed combination) does not occur before the selective heating step. In particular, Zanzucchi teaches that, in those wells in which heating is to occur, the reaction mixture must be held and sealed within the well (*see, e.g.*, col. 9, lines 34-54). In addition, Zanzucchi appears to teach that each of the wells allows for an action upon a product from the previous well, suggesting that Zanzucchi's method is very different from the claimed method.

Thus, Zanzucchi actually teaches flowing a mixture into one well (which, according to the Examiner's proposal would contain a first substrate), allowing binding, sealing the well, heating the well, and flowing the mixture into a second well (which would contain a second substrate). At best, the Examiner's proposed combination might teach this process; however, this is very different from the claimed method, in which the mixture is flowed through each of the solid supports (step a), prior to the selective heating/dissociation (step b). Applicants note that the Examiner has not addressed this aspect of the claimed method and thus, a *prima facie* case of obviousness has not been established. Moreover, neither the cited references, nor the Examiner's proposed combination demonstrate how or why such an aspect could or should be implemented.

Applicants note that this particular element has numerous advantages, as it allows for parallel and rapid collection/separation/elution of different polynucleotides via a single completely serial arrangement. This arrangement allows for the complete starting volume of a sample to effectively be used across each solid support. Thus, the complete volume of a single sample can effectively be run "in parallel" on a single linear system by using the claimed method. In contrast, the devices and methods outlined by the Examiner either use combined parallel and serial systems or arrays for processing (such as Fig. 8A in Zanzucchi, which divide up starting material initially) or use their entire array as a parallel system, across which the sample is eventually evenly distributed (and thus less of the sample interacts with the binding partners. See Fig. 1, Okano and Fig. 2A, Brenner). The presently claimed invention combines the advantages of serial flow (higher concentration/movement of the complete solution across/through each solid support) with the advantages of parallel techniques (greater diversity of collection, larger collection sizes, etc) in a manner so that the advantages of each technique can be realized. This is clearly a superior aspect over the embodiments disclosed in the cited art (and suggested by the Examiner), which are not arranged for such a result.

As the cited references and proposed combination thereof do not demonstrate the combination of step b) following step a), not all of the elements have been taught and a *prima facie* case of obviousness has not been established with regard to Claim 21 and its dependent claims.

B. The Examiner has Not Demonstrated that there Would be a Reasonable Expectation of Success in his Proposed Combination.

In the Final Office Action, the Examiner has simply asserted that "[i]n view of the well-developed state of the art, said ordinary artisan would have had a most reasonable expectation of success." (Final Office Action, p. 6). However, the Examiner has not explained what this means or why that expectation would be there. Indeed, Applicants submit that, for at least some of Zanzucchi's embodiments, it is clear there would not have been an expectation of success in the Examiner's combination, as demonstrated by Zanzucchi itself.

As noted above, in Zanzucchi the flow of the mixture is controlled by the closing of valves in channels. Zanzucchi teaches that these valves are required for the device to function

(or else the fluid leaves the chamber when heated)[1]. Applicants note that, in many embodiments, Zanzucchi teaches that the increase in temperature of the wells results in the sealing of the wells by the valves (col. 9, lines 38-54). Thus, it is clear from the teachings in Zanzucchi that, at least in some embodiments, elevated temperatures will keep wells closed and prevent a mixture from flowing out until the mixture cools. While this is not problematic for Zanzucchi's embodiments, it would be problematic for the Examiner's proposed modification of Zanzucchi. In particular, if the wells include polynucleotides bound to a solid support, when that well is heated the well will become sealed.[2] More importantly, the valves will not open until the solution cools. This is problematic for the Examiner's proposed combination because even though the heat may, temporarily, allow for the release of the polynucleotides, the mixture cannot be eluted out (as recited in step c of Claim 21) because the well is sealed. Additionally, as is known by those of skill in the art, cooling the mixture in the well will result in the rehybridization of the polynucleotide to the solid support, which can prevent the polynucleotide from flowing out once the valves are opened.

In light of the above issues, it is clear that, one of skill in the art, using various embodiments of Zanzucchi, would not have necessarily expected the combination to work because the device in Zanzucchi will not necessarily allow for the elution of the finished product as claimed.[3]

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[1] "Because of the high temperatures required in the last two steps, a significant vapor pressure may develop in the first well 36, causing a back pressure in both directions--back toward the sample loading channel 34 and forward to the succeeding second well 40. Thus preformed valves 62 and 63 as shown in FIG. 6A...are preloaded into the channel 38." (3rd paragraph, Example 1)

[2] Applicants note that Zanzucchi does teach other valves; however, the Examiner has not supplied a reason for selecting the other valves and it is clear from the reference that the valves are not art recognized equivalents as they have different, and particular important, properties.

[3] Applicants note that the valves appear to be important for those wells in which a temperature change is to occur. (*See, e.g.*, Example 1).

C. There are Significant Differences Between the Cited Art and the Claimed Invention

In addition to the specific differences between the Examiner's proposed combination and the presently claimed invention noted above, Applicants also note that, as a whole, there are significant differences between the teachings in the art and the claimed invention.

Brenner Teaches Away from the Examiner's Proposed Combination

The Examiner stated "it would have obvious... to have combined the microparticles of Brenner in the individual cells of the array of Okano, with the series of wells/array of Zanzucchi..." (Final Office Action, page 6). Applicants do not agree with this assertion.

The Examiner has attempted to combine or modify the teachings in Brenner, involving a process that is explicitly parallel, with a serial embodiment in order to obtain an element of the presently claimed invention (*e.g.*, the "mixture flows serially though each of the plurality of solid supports"). Such a combination is improper as it would defeat the purpose of the array in Brenner and because Brenner teaches away from such a modification.

Brenner explicitly states that "[a]n important feature of my invention is the capability of applying the method to many different polynucleotides in parallel..." (col. 3, lines 46-62 of Brenner, emphasis added, *see also*, col. 2, lines 24-30; col. 4, lines 60-67; and col. 7, lines 10-20). Thus, Brenner actually teaches that his microparticles should be used in parallel applications and he teaches away from a serial (or purely linear) arrangement. As appreciated by the Examiner, it is improper to "combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)" (M.P.E.P. §2145 (X)(D)(2)) or where the modification would change the principle of operation of the references.[4] Not only does Brenner generally teach away from stepwise serial embodiments, but the application of Brenner's microparticles in a serial application would remove the simultaneous/parallel aspect taught in Brenner as an important advantage of his invention. As such, the combination of Brenner with Zanzucchi as proposed by the Examiner, is

[4] "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)" M.P.E.P. §2143.01.

clearly improper. Applicants note that the fact that the combination may be relevant to the elements recited in the claims is moot, as the combination is impermissible in this situation.

There is no Reason to Combine a) Okano and b) Brenner and/or Zanzucchi

Applicants note that the Examiner, while relying on Okano for some teachings, has identified no reason why one of skill in the art would have used the cited teachings of Okano in combination with Brenner and/or Zanzucchi. Applicants respectfully remind the Examiner that, in order to establish a *prima facie* case of obviousness, it is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. In the instant Office Action, no reason has been provided. As such, a *prima facie* case of obviousness has not been established.

Moreover, Applicants submit that there does not appear to be a reason to make the Examiner's proposed combination of the microparticles of Brenner with the individual cells of Okano because the substrate (microparticles) in the Brenner reference would be redundant to the substrate (electrode surface) in the Okano reference. Because it would be redundant, one of skill in the art would not have been prompted to combine these aspects as asserted by the Examiner.

As such, the Examiner has failed to identify an adequate reason for combining the various components noted in the cited references. As such, a *prima facie* case of obviousness has not been established.

Because not all of the elements have been taught, the Examiner has not demonstrated that one of skill in the art would have reasonably expected the combination to work, and the Examiner has not identified proper or sufficient reasons to combine the cited references, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and the claims allowed. As appreciated by the Examiner, the dependent claims, while nonobvious for the reasons noted above in regard to the independent claims, also recite additional elements that further distinguish them from the cited art (some of which are noted below).

Errors of Law and Procedure

- The Examiner has improperly combined Brenner and Zanzucchi, as Brenner teaches away from the purely serial aspect cited in Zanzucchi.
- The Examiner has not addressed each of the pending claims. It appears as though the Examiner has primarily addressed Claim 21 on the merits, discounting elements in the dependent claims, such as specific shapes in the channel and flow path, as "obvious design choice." However, the Examiner has supplied no support for this general assertion. Applicants note that the art cited by the Examiner is generally directed to microfluidic/microelectronic devices for the detection and/or manipulation of very small amounts of nucleic acid sequences. In contrast, the presently claimed device is directed to serial, efficient, collection and isolation of polynucleotides. There appears to be little or no reason for why the technology cited by the Examiner would benefit from the additional elements recited in the dependent claims. Thus, these dependent claims establish further points of nonobviousness over the cited art. Applicants request that support for the Examiner's assertions be made of record (*e.g.*, the Examiner can make official notice of such teachings) or withdraw the rejections of the dependent claims.

  Moreover, Applicants note that the specific items in the dependent claims are valuable for the Applicants' claimed techniques. For example, the elements in Claims 30-33 result in a method in which the entirety of the mixture flows through each of the solid supports; thereby ensuring that as much of the mixture is screened as possible prior to the mixture passing out of the solid support and into the next solid support. This results in a superior advantage over other possible configurations. Similarly, Claims 34-37 recite aspects that yield advantageous results for the purification aspects of the presently claimed method, but are, relatively speaking, inapplicable to the microelectronic devices (Okano and Zanzucchi) and two-dimensional arrays (Brenner) cited by the Examiner. As such, these elements clearly result in patentable distinctions over the cited art. Thus, the dependent claims do supply superior aspects and inventiveness to the claimed invention and are entitled to a proper examination by the Examiner.

  Applicants also note that the Examiner's reference to the Applicants' own work is improper, as the Applicants' disclosure cannot be used against them in demonstrating

obviousness. The cited section only demonstrates that the Applicants appreciated the value of these variables, and does not establish that, prior to the instant filing, anyone else would have necessarily understood these options.

Incorrect Factual Characterizations:

- Zanzucchi does not appear to teach the continuous/serial arrangement of flowing through all of the supports in the flow path prior to acting on each of the supports separately. Instead, at best, Zanzucchi might teach a sequential method of using each of the separate wells serially (flowing, dehybridizing, flowing, dehybridizing, etc).
- Zanzucchi does not appear to teach that the beads are present in each well. Zanzucchi, while teaching the option of beads (*e.g.*, a solid support) in one well, does not teach the presence of solid supports (through which the mixture can flow) simultaneously in multiple wells.
- Okano does not teach that heating can be used for specific elution. Okano, at best, might teach that heating can be used for general elution. Okano teaches that an electric field (in combination with general heat) can be used for specific elution (although in a manner very different from what is presently claimed).
- The Examiner has mischaracterized the claimed invention on page 3 of the Office Action. The Examiner has interpreted the claimed invention as involving "...two different capture moieties...bound at two different locations on a support...". In contrast, the claims recite that each support has "a sequence-specific capture agent complementary to a different-sequence polynucleotide...". Thus, the claims require that the different capture agents be present on different supports. The Examiner does not appear to have addressed this element in his rejections.
- The Examiner has mischaracterized the claimed invention on page 3 of the Office Action. The Examiner has interpreted the support as acting as a "flow path". However, Applicants note that the claims clearly recite that this is not the case. Rather, the "flow path...[contains] a plurality of solid supports..." Applicants do note that the mixture also flows through the solid supports.

Clarification of Previous Points Made by Applicant

Applicants note that the Examiner did not seem to fully appreciate the Applicants' separate arguments regarding 1) the combination of a) Okano and b) Brenner and/or Zanzucchi and 2) the adequacy of the Examiner's motivation to combine Brenner and Zanzucchi.(pages 10 and 11, previous Response). The Examiner appears to have interpreted these two issues as refuting one another (see page 7, item 22, Final Office Action). The Examiner may have misread Applicants' arguments. In the argument indicated by the Examiner as the first argument, Applicants argued that there is no motivation for combining Brenner with Okano and Zanzucchi, because the substrate (microparticles) in Brenner would be redundant to the substrate (electrode surface) in the Okano reference. The emphasis of this argument is the redundancy of the substrates from Brenner and Okano.

In the argument indicated by the Examiner as the second argument, Applicants argued that the proposed motivation to combine Brenner and Zanzucchi is inadequate for other reasons. As stated in the previous response, the mere fact that Zanzucchi can be used in some DNA hybridization assays and that Brenner can be used in DNA hybridization assays supplies no reason for the combination and modification of particular subparts of Brenner (a two-dimensional microparticle array system) into a well format taught in Zanzucchi. The emphasis of this argument is on the lack of reason to combine Brenner and Zanzucchi. Applicants do not see these arguments as exclusive of one another.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and request the same. If, however, some issue remains that the Examiner feels can be addressed by Examiner Amendment, the Examiner is cordially invited to call the undersigned for authorization.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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